PATENT CLAIMS

1. A process for producing parenterally administrable microparticles containing a biologically active substance, which process comprises:

a) preparing an aqueous solution of the biologically active substance to be incorporated in the microparticles,

b) mixing the solution obtained in step a) with an aqueous solution of polyethylene glycol (PEG) under such conditions that the biologically active substance is concentrated and/or solidified,

c) optionally washing the concentrated and/or solidified biologically active substance obtained in step b),

d) mixing the concentrated and/or solidified biologically active substance obtained in step b) or c) with an aqueous starch solution,

e) mixing the composition obtained in step d) with an aqueous solution of a polymer having the ability of forming a two-phase aqueous system, so as to form an emulsion of starch droplets which contain the biologically active substance as the inner phase in an outer phase of said polymer solution,

f) causing or allowing the starch droplets obtained in step e) to solidify into starch microparticles,

g) drying the starch microparticles from step f), and

h) optionally applying a release controlling shell of a biocompatible and biodegradable polymer to the dried starch microparticles from step f).

2. A process according to claim 1, in which step b) is performed such that the solidification of the biologically active substance leads to precipitation of the same.

3. A process according to claim 1, in which step b) is performed such that the solidification of the biologically active substance results in a highly viscous solution, which has the ability of forming droplets which can be handled at room temperature.

4. A process according to claim 1, in which step b) is performed to a reversibly solidified active substance.

5. A process according to claim 1, in which the solidified biologically active substance forms a pellet or a highly viscous or solid bottom phase in centrifugation or ultracentrifugation.

6. A process according to claim 1, in which the polyethylene glycol used in step b) has an average molecular weight of 400-100,000 Da, preferably 4 000-35 000 Da, more preferably 6 000-20,000 Da, and most preferably about 20,000 Da.

7. A process according to claim 1, in which the concentration of the polyethylene glycol used in step b) is in the range of 1-50 % (w/w), preferably 2-45 % (w/w), more preferably 10-40 % (w/w), and most preferably 20-35 % (w/w).

8. A process according to claim 1, in which in step d) an aqueous starch solution is utilized, comprising starch which has an amylopectin content exceeding 85% by weight, in which the molecular weight of the said amylopectin has been reduced such that at least 80% by weight of the material lies within the range of 10-10 000 kDa.

9. A process according to claim 1, in which in step d) an aqueous starch solution is utilized, comprising starch which has an amino acid nitrogen content of less than 50 µg per g dry weight of starch.

10. A process according to claim 1, in which the starch concentration of the aqueous starch solution used in step d) is at least 20% by weight.

11. A process according to claim 8, in which the starch has a purity of at most 20 µg, preferably at most 10 µg, and more preferably at most 5 µg, amino acid nitrogen per g dry weight of starch.

12. A process according to claim 8, in which the starch has an amylopectin content with said reduced molecular weight exceeding 95% by weight, preferably exceeding 98% by weight.

13. A process according to claim 8, in which the molecular weight of said amylopectin has been reduced such that at least 80% by weight of the material lies within the range of 100-4 000 kDa, preferably 200- 1 000 kDa, and more preferably 300-600 kDa.

14. A process according to claim 1, in which the starch is such that it can be dissolved to a concentration exceeding 25% by weight in water.

15. A process according to claim 1, in which the starch is substantially lacking in covalently bonded extra chemical groups of the types which are found in hydroxyethyl starch.

16. A process according to claim 1, in which the starch has an endotoxin content of less than 25 EU/g and contains less than 100 microorganisms per g.

17. A process according to claim 1, in which the starch is essentially purified from surface-located proteins, lipids and endotoxins by means of washing with an aqueous alkali solution and purified from internal proteins by means of ion-exchange chromatography, preferably anion-exchange chromatography.

18. A process according to claim 8, in which in step d) 2-15% by weight amylose is also used as starch, having an average molecular weight within the range of 2.5-70 kDa, preferably 5-45 kDa, in which the percentage by weight is calculated on the basis of dry weight starch.

19. A process according to claim 8, in which in step d) a solution is prepared having a starch concentration of at least 30% by weight.

20. A process according to claim 8, in which in step d) a solution is prepared having a starch concentration of at most 50% by weight, preferably at most 45% by weight.

21. A process according to claim 8, in which the aqueous starch solution in step d) is prepared with accompanying autoclaving.

22. A process according to claim 1, in which in step d) the active substance is combined with the starch solution at a temperature of at most 60°C, preferably 20-45°C, especially 30-37°C.

23. A process according to claim 1, in which in step d) a composition is formed in which the weight ratio between starch and biologically active substance lies within the range of 3:1 to 10 000:1.

24. A process according to claim 1, in which the mixing in step e) is performed at a temperature within the range of 4-50°C, preferably 10-40°C, especially 10-37°C.

25. A process according to claim 1, in which the mixing in step e) is performed by means of at least one static mixer.

26. A process according to claim 1, in which in step e) the polymer solution is added to the composition in at least two steps, at least one of the additions being effected after the emulsion has begun to be created.

27. A process according to claim 1, in which in step e) polyethylene glycol is used as the aqueous polymer.

28. A process according to claim 27, in which the polyethylene glycol has an average molecular weight of 5-35 kDa, preferably 15-25 kDa, especially ca. 20 kDa.

29. A process according to claim 1, in which in step e) starch droplets are formed which give the size required for the microparticles, preferably a mean particle diameter, in the dry state, within the range of 10-200 µm, preferably 20-100 µm, more preferably 20-80 µm.

30. A process according to claim 29, in which after step e) the microparticles are washed, through filtration, and optionally sieved in order to obtain the desired particle size distribution.

31. A process according to claim 1, in which the solidification in step f) is effected at at least two temperatures, in which the initiation is effected at a lower temperature than the termination.

32. A process according to claim 31, in which the solidification is initiated within the range of 1-20°C, preferably 1-10°C, especially around 4°C, and is terminated within the range of 20-55°C, preferably 25-40°C, especially around 37°C.

33. A process according to claim 1, in which the drying in step g) is performed in the form of spray-drying, freeze-drying or vacuum-drying, preferably freeze-drying.

34. A process according to claim 1, in which, as the biologically active substance, a substance is incorporated which is chosen from the group consisting of proteins, peptides, polypeptides, polynucleotides and polysaccharides, especially recombinantly produced proteins.

35. A process according to claim 1, in which the application of the release-controlling shell in step h) is performed by means of air suspension technology.

36. A process according to claim 1, in which the release-controlling shell in step h) is formed by a homopolymer or copolymer containing alpha-hydroxy acid units.

37. A process according to claim 36, in which the alpha-hydroxy acid is lactic acid and/or glycolic acid.

38. Microparticles suitable for parenteral administration, preferably via injection, to a mammal, especially a human being, and containing a biologically active substance, which microparticles essentially consist of parenterally administrable, biodegradable starch as a matrix, which contains the biologically active substance in essentially non-chemically complex-bonded form and in the form of solid particles having a mean size within the range of 0.05-30 µm.

39. Microparticles according to claim 38, in which the biologically active substance is a precipitated substance.

40. Microparticles according to claim 38, in which the particles of the biologically active substance have a mean size within the range of 0.2-10 µm, preferably 0.5-5 µm, more preferably 1-4 µm.

41. Microparticles according claim 38, in which the starch has an amylopectin content exceeding 85% by weight, of which at least 80% by weight has an average molecular weight within the range of 10-1 000 kDa.

42. Microparticles according to claim 38, in which the starch has an amino acid nitrogen content of less than 50 µg per g dry weight starch and which microparticles have no covalent chemical cross-linking between the starch molecules.

43. Microparticles according to claim 38, in which the starch is of the kind defined in claim 6.

44. Microparticles according to claim 138, which have a release-controlling shell obtained or formed according to claim 35.

45. Microparticles according to claim 38, in which the bioactivity of the biological substance is at least 80%, preferably at least 90% and most preferably

essentially maintained compared with the bioactivity exhibited by the substance prior to its incorporation in the starch.

46. Microparticles according to claim 38, which are biodegradable in vitro in the presence of alpha-amylase and/or amyloglucosidase.

47. Microparticles according to claim 38, which are biodegradable and are eliminated from tissue after subcutaneous or intramuscular administration.

48. Microparticles according to claim 38, in which the biologically active substance is chosen from the group consisting of proteins, peptides, polypeptides, polynucleotides and polysaccharides.

49. Microparticles according to claim 48, in which the protein is a recombinantly produced protein.

50. Microparticles according to claim 48, in which the protein is chosen from amongst growth hormones, colony-stimulating factors, erythropoietins, interferons, insulin and vaccines.

51. Microparticles according to claim 50, in which the protein is a growth hormone.

52. Microparticles according to claim 51, in which the growth hormone is human growth hormone (hGH).

53. Microparticles according to claim 38, in which the divalent metal ions content is such that the molecular ratio of total metal cations: biologically active substance is less than 0.2:1, preferably less than 0.1:1, more preferably less than 0.01:1.

54. Microparticles according to claim 53, in which the quoted molecular ratios apply to zinc as the said metal.

55. Microparticles according to claim 52, in which the dimers content of the human growth hormone is <2% by weight, preferably <1% by weight and the polymers content is <0.2% by weight, preferably <0.1% by weight.

56. Microparticles according to claim 52, in which the release kinetics for hGH determined in vitro are characterized by substantially continuous and regular release over at least one week.

57. Microparticles which are obtainable by means of a process according to any one of claim 1.